



DATE: 07-Aug-2018  
TO: Heather Wachtel  
CC:

**Institutional Review Board**  
3800 Spruce St., First Floor Suite 151  
Philadelphia, PA 19104  
Phone: 215-573-2540  
(Federalwide Assurance # 00004028)

RE:  
IRB PROTOCOL#: 829615  
PROTOCOL TITLE: Circulating microRNA signatures in primary hyperparathyroidism  
  
SPONSOR: NO SPONSOR NUMBER  
REVIEW BOARD: IRB #7

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#### **IRB AMENDMENT: NOTICE OF APPROVAL**

Dear Dr. Wachtel,

The documents noted below, for the above-referenced protocol, were reviewed by the Institutional Review Board using the expedited procedure set forth in 45 CFR 46.110 and approved on 06-Aug-2018.

This study has been determined to pose minimal risk to subjects. IRB approval for the study will expire on 29-May-2019.

The documents included with the application noted below are approved: -HSERA Modification,

confirmation code: cgjgbggf, submitted 7/31/2018

#### **ONGOING REQUIREMENTS:**

- You must obtain IRB review and approval under 45 CFR 46 if you make any changes to the protocol, consent form, or any other study documents subject to IRB review requirements. Implementation of any changes cannot occur until IRB approval has been given.
- Reportable event, such as serious adverse events, deviations, potential unanticipated problems, and reports of non-compliance must be reported to the IRB in accordance with Penn IRB SOP RR 404.
- When enrolling subjects at a site covered by the University of Pennsylvania's IRB, a copy of the IRB approved informed consent form with the IRB approved from/to stamp must be used unless a waiver of written documentation of consent has been granted.

COMMITTEE APPROVALS: You are responsible for assuring and maintaining other relevant committee approvals. This human subjects research protocol should not commence until all relevant committee approvals have been obtained.

If your study is funded by an external agency, please retain this letter as documentation of the IRB's determination regarding your proposal.

If you have any questions about the information in this letter, please contact the IRB administrative staff. A full listing of staff members and contact information can be found on our website: <http://www.irb.upenn.edu>

\*\*\*This letter constitutes official University of Pennsylvania IRB correspondence. \*\*\*

# Modification

## Basic Info

Confirmation Number: **cgjgbggf**

Protocol Number: **829615**

Created By: **WACHTEL, HEATHER**

Principal Investigator: **WACHTEL, HEATHER**

Protocol Title: **Circulating microRNA signatures in primary hyperparathyroidism**

Short Title: **miRNA in primary hyperparathyroidism**

Protocol Description: **The goal of this study is to: 1. Analyze the expression levels of circulating (serum) miRNAs in primary hyperparathyroidism patients with and without osteoporosis, and patients with osteoporosis undergoing thyroidectomy, and to correlate with clinical markers of bone remodeling including biochemical and radiologic studies. 2. To evaluate serum miRNA levels after treatment with parathyroidectomy.**

Submission Type: **Biomedical Research**

Application Type: **EXPEDITED Category 2**

## PennERA Protocol Status

Approved

Resubmission\*

No

Are you submitting a Modification to this protocol?\*

Yes

## Current Status of Study

Study Status

Study has not begun (no subjects entered)

*If study is currently in progress, please enter the following*

Number of subjects enrolled at Penn since the study was initiated

0

Actual enrollment at participating centers

0

***If study is closed to further enrollment, please enter the following***

**Number of subjects in therapy or intervention**

0

**Number of subjects in long-term follow-up only**

0

**IRB Determination**

If the change represents more than minimal risk to subjects, it must be reviewed and approved by the IRB at a convened meeting. For a modification to be considered more than minimal risk, the proposed change would increase the risk of discomfort or decrease benefit. The IRB must review and approve the proposed change at a convened meeting before the change can be implemented unless the change is necessary to eliminate an immediate hazard to the research participants. In the case of a change implemented to eliminate an immediate hazard to participants, the IRB will review the change to determine that it is consistent with ensuring the participant's continued welfare. Examples: Convened Board Increase in target enrollment for investigator initiated research or potential Phase I research Expanding inclusion or removing exclusion criteria where the new population may be at increased risk Revised risk information with active participants Minor risk revisions that may affect a subject's willingness to continue to participate Expedited Review Increase in target enrollment at Penn where overall enrollment target is not exceeded or potentially sponsored research Expanding inclusion or removing exclusion where the new population has the same expected risk as the previous, based on similarities of condition Revised risk information with subjects in long-term follow-up Minor risk revisions with no subjects enrolled to date Expedited Review

**Modification Summary**

Please describe any required modification to the protocol. If you are using this form to submit an exception or report a deviation, enter 'N/A' in the box below.

This modification is to: 1. Make changes to the PRA template based on updated cost estimates for specimen processing. 2. Revise location of labs which are performing specimen processing. These will be processed in a deidentified manner at the Translational Core Lab at CHOP (Penn internal lab) as UPHS does not offer several of the tests internally and we would be required to send them to ARUP labs (external lab).

**Risk / Benefit**

Does this amendment alter the Risk/Benefit profile of the study?

No

**Change in Consent**

Has there been a change in the consent documents?

No

**If YES, please choose from the options below regarding re-consenting**

**Deviations**

**Are you reporting a deviation to this protocol?\***

No

## Exceptions

Are you reporting an exception to this protocol?\*

No

## Protocol Details

Resubmission\*

Yes

## Study Personnel

### *Principal Investigator*

Name:	WACHTEL, HEATHER
Dept / School / Div:	4502 - SU-Surgery Administration
Campus Address Mail Code	6070
Address:	HARRISON - 313 STMLR 3450 HAMILTON WK
City State Zip:	PHILADELPHIA PA 19104-6070
Phone:	215-519-8058
Fax:	215-662-7983
Pager:	
Email:	Heather.Wachtel@uphs.upenn.edu
HS Training Completed:	Yes
Training Expiration Date:	09/22/2018
Name of course completed :	CITI Protection of Human Subjects Research Training - ORA

### *Study Contacts*

None

### *Other Investigator*

Name:	LEVINE, MICHAEL
Dept / School / Div:	7 - General University EB Pool
Campus Address Mail Code	4399
Address:	Suite 30 34th and Civic Cente 11 Northwest Tower (CHOP)
City State Zip:	Philadelphia PA 19104-4399

Phone:	<b>215-590-3618</b>
Fax:	-
Pager:	
Email:	<b>levinem@email.chop.edu</b>
HS Training Completed:	<b>Yes</b>
Training Expiration Date:	<b>07/19/2018</b>
Name of course completed :	<b>CITI Protection of Human Subjects Research Training - ORA</b>

**Responsible Org (Department/School/Division):**

4502 - SU-Surgery Administration

***Key Study Personnel***

Name:	<b>RAPAPORT KELZ, RACHEL</b>
Department/School/Division:	<b>SU-Surgery Administration</b>
HS Training Completed:	<b>Yes</b>
Training Expiration Date:	<b>09/29/2020</b>
Name of course completed:	<b>CITI Protection of Human Subjects Research Training - ORA</b>
Name:	<b>ERMER, JAE P</b>
Department/School/Division:	<b>SU-Surgery Administration</b>
HS Training Completed:	<b>Yes</b>
Training Expiration Date:	<b>12/03/2020</b>
Name of course completed:	<b>CITI Protection of Human Subjects Research Training - ORA</b>
Name:	<b>FRAKER, DOUGLAS L</b>
Department/School/Division:	<b>SU-Surgery Administration</b>
HS Training Completed:	<b>Yes</b>
Training Expiration Date:	<b>05/06/2019</b>
Name of course completed:	<b>CITI Protection of Human Subjects Research Training - ORA</b>
Name:	<b>AL MUKADDAM, MONA</b>
Department/School/Division:	<b>DM-Endocrinology, Diabetes &amp; Metabolism</b>
HS Training Completed:	<b>Yes</b>
Training Expiration Date:	<b>03/28/2020</b>
Name of course completed:	<b>CITI Protection of Human Subjects Research Training - ORA</b>

**Disclosure of Significant Financial Interests\***

Does any person who is responsible for the design, conduct, or reporting of this research protocol have a **FINANCIAL INTEREST**? No

**Penn Intellectual Property\***

To the best of the Principal Investigator's knowledge, does this protocol involve the testing, development or evaluation of a drug, device, product, or other type of intellectual property (IP) that is owned by or assigned to the University of Pennsylvania?

No

**Certification**

I have reviewed the *Financial Disclosure and Presumptively Prohibited Conflicts for Faculty Participating in Clinical Trials* and the *Financial Disclosure Policy for Research and Sponsored Projects* with all persons who are responsible for the design, conduct, or reporting of this research; and all required Disclosures have been attached to this application.

Yes

## Biomedical Research

**Clinical Trial\***

Is this a clinical trial?

No

**Investigator Initiated Trial\***

Is this an investigator initiated trial?

No

**Drugs or Devices\***

Does this research study involve Drugs or Devices?

No

**IND Exemption**

**For studies that fall under an IND exemption, please provide the number below**

**For studies including IND or IDE's, please provide the number(s) below**

**IDE Review\***

NOTE: For research involving investigational devices, you are required to review the guidance on Managing Research Device Inventory. Consult the Penn Manual for Clinical Research: [https://www.med.upenn.edu/pennmanual/secure/investigational-product-management-at-sites-not-using-investigational-drug-services-\(ids\).html](https://www.med.upenn.edu/pennmanual/secure/investigational-product-management-at-sites-not-using-investigational-drug-services-(ids).html) Please check the box Yes if you have reviewed the guidance.

Yes

**Research Device Management\***

Please indicate how research device(s) will be managed.

Not Applicable (no investigational devices)

**Drug, Herbal Product or Other Chemical Element Management \***

Please indicate how drugs, herbal products or other chemical entities will be managed.

Not Applicable (no drugs, herbal products or other chemical entities)

**Radiation Exposure\***

Are research subjects receiving any radiation exposure (e.g. X-rays, CT, Fluoroscopy, DEXA, pQCT, FDG, Tc-99m, etc.) that they would not receive if they were not enrolled in this protocol?

No

**Gene Transfer\***

Does this research involve gene transfer (including all vectors) to human subjects?

No

**Human Source Material\***

Does this research include collection or use of human source material (i.e., human blood, blood products, tissues or body fluids)? Yes

**CACTIS and CT Studies\***

Does the research involve Center for Advanced Computed Tomography Imaging Services (CACTIS) and CT studies that research subjects would not receive if they were not part of this protocol?

No

**CAMRIS and MRI Studies\***

Does the research involve Center for Advanced Magnetic Resonance Imaging and Spectroscopy (CAMRIS) and MRI studies that research subjects would not receive if they were not part of this protocol?

No

**Investigational Agent or Device within the Operating Room\***

Does the research project involve the use of an investigational agent or device within the Operating Room?

No

**Cancer Related research not being conducted by an NCI cooperative group\***

Does this protocol involve cancer-related studies in any of the following categories?

No

**Processing of Materials\***

Will the research involve processing (such as over encapsulating, or compounding)?

No

**In-House Manufacturing of Materials\***

Will the research involve processing (such as over encapsulating, or compounding)?

No

**Medical Information Disclosure\***

Does the research proposal involve the use and disclosure of research subject's medical information for research purposes? Yes

**If the answer is YES, indicate which items is is provided with this submission:**

Modified research informed consent document that incorporates HIPAA requirements

**CTRC Resources\***

Does the research involve CTRC resources?

No

**Pathology and Laboratory Medicine Resources\***

Will samples be collected by hospital phlebotomy and/or processed or analyzed by any of the clinical laboratories of the University of Pennsylvania Health System? Yes

**Clinical Laboratory Services\***

Will samples be collected by UPHS phlebotomy and/or analyzed by the hospital laboratory? Yes

**Anatomic Pathology Services\***

Will tissue specimens (other than blood) be collected for clinical, diagnostic, or research purposes OR be processed through surgical pathology, cytopathology, neuropathology, or hematopathology?

No

**Research Involves Apheresis, Cell Collection, and/or Blood Product Collection\***

Does this research involve collection of blood products in the Penn Donor Center and/or the use of apheresis for treatment or collection of cells or other blood components?

No



**Research involving blood transfusion or drug infusions\***

Will your research involve blood transfusion or infusion of study drug in 3 Ravdin Apheresis Unit for research purposes?

No

**Trial in Radiation Oncology**

Is this research a prospective trial being done in Radiation Oncology, and if so, has this protocol been approved by the Radiation Oncology Protocol committee?

N/A

**Study in Radiation Oncology**

Is this research a retrospective study being done in Radiation Oncology, and if so, has this project been reviewed by the Radiation Oncology Clinical Research Group?

N/A

**Use of UPHS services\***

Does your study require the use of University of Pennsylvania Health System (UPHS) services, tests or procedures\*, whether considered routine care or strictly for research purposes?

Yes

**Primary Focus\***

Tissue/biospecimen

**Protocol Interventions**

Sociobehavioral (i.e. cognitive or behavioral therapy)

Drug

Device - therapeutic

Device - diagnostic (assessing a device for sensitivity or specificity in disease diagnosis) Surgical

Diagnostic test/procedure (research-related diagnostic test or procedure)

☒ Obtaining human tissue for basic research or biospecimen bank

Survey instrument

None of the above

The following documents are currently attached to this item:

*There are no documents attached for this item.*

**Sponsors****Business Administrator**

Name:	MERVIS, STEVEN
Dept / School / Div:	4502 - SU-Surgery Administration
Phone:	215-662-2806
Fax:	-
Pager:	
Email:	steve.mervis@uphs.upenn.edu

**Department budget code**

400 - 400 - 1 - 461243 - XXXX - 2433 - 4498

### ***Funding Sponsors***

#### **Funding sponsors billing address**

If you have selected a commercial or industry sponsor, please provide the appropriate address and contact information for the Sponsor for the purposes of billing for IRB review fees (initial review, continuing review and convened modification fees apply here). If the Sponsor is not industry/ commercial, this information is not necessary to provide with your application.

#### **Funding sponsors gift**

Is this research being funded by a philanthropic gift?

### ***Regulatory Sponsor***

#### **IND Sponsor**

none

400 - 400 - 1 - 461243 - XXXX - 2433 - 4498

#### **Industry Sponsor**

None

#### **Project Funding\***

Is this project funded by or associated with a grant or contract?

No

#### **Sponsor Funding**

Is this study funded by an industry sponsor?

#### **Status of contract**

**The following documents are currently attached to this item:**

*There are no documents attached for this item.*

## **Multi-Site Research**

### ***Other Sites***

No other sites

#### **Management of Information for Multi-Center Research The**

**following documents are currently attached to this item:**

*There are no documents attached for this item.*

## **Protocol**

### **Abstract**

PHPT disproportionately affects post-menopausal women at elevated risk for osteoporosis. Surgery is indicated for asymptomatic patients with skeletal manifestations of osteoporosis and pathologic fractures, but not for those with osteopenia. However, more than a third of patients with asymptomatic PHPT demonstrate progressive disease, and meeting criteria for surgery at initial diagnosis is not predictive of disease progression. Although clinical tools are available to estimate the probability of major osteoporotic

fracture, no biochemical markers for risk stratification exist. Serum miRNAs have both diagnostic and prognostic potential, to assist in identification of PHPT patients at elevated fracture risk and to determine subpopulations who may benefit from surgical parathyroidectomy.

## **Objectives**

### **Overall objectives**

The goal of this study is to: 1. Analyze the expression levels of circulating (serum) miRNAs in primary hyperparathyroidism patients with and without osteoporosis, and to correlate with clinical markers of bone remodeling including biochemical and radiologic studies. 2. To evaluate serum miRNA levels after treatment with parathyroidectomy.

### **Primary outcome variable(s)**

Primary outcome variable: Serum miRNA levels

### **Secondary outcome variable(s)**

Secondary outcome variables: Clinical markers of bone remodeling, including serum levels of bone-specific alkaline phosphatase, osteocalcin, P1NP, CTX, calcium, phosphate, vitamin D metabolites, and PTH; urine calcium; and DXA scan.

## **Background**

Osteoporosis and osteopenia are chronic diseases disproportionately affecting the elderly. In the United States, the prevalence of osteoporosis is projected to increase from 10 million in 2005 to 14 million in 2025, due to population aging.<sup>1,2</sup> Similarly, the economic cost of osteoporotic fractures is projected to increase to \$25 billion by 2025. Primary hyperparathyroidism (PHPT) is one of the few reversible causes of osteoporosis and fragility fractures. PHPT is the third most common endocrine disorder, with an incidence of 27-30 per 100,000 person-years, and increasing with age; half of all patients with PHPT are post-menopausal women, a population at high risk for osteoporosis at baseline.<sup>3</sup> All forms of PHPT are characterized by loss of the normal negative feedback relationship between serum calcium and parathyroid hormone (PTH) secretion, leading to hypercalcemia and hyperparathyroidism. Classic PHPT is characterized by skeletal, renal, gastrointestinal and neuropsychiatric manifestations. Skeletal manifestations of classic PHPT are mediated by osteoblast inhibition and osteoclast stimulation, leading to increased bone remodeling.<sup>4</sup> The catabolic effects of chronic PTH excess may present as osteitis fibrosa cystica, brown tumors, pathologic fractures, bone pain, osteoporosis or osteopenia. Although frank osteitis fibrosa cystica is an increasingly rare presentation of PHPT in the United States, affecting 2% of patients, osteoporosis is reported in 39-63% of patients, with preferential loss of bone density in cortical sites.<sup>5</sup> Fragility fractures are significantly associated with PHPT, particularly in postmenopausal women.<sup>6,7</sup> Both decreases in bone mineral density (BMD) and fragility fractures are considered indications for parathyroidectomy in patients with asymptomatic PHPT.<sup>8</sup> Parathyroidectomy has been demonstrated to improve BMD in prospective studies of PHPT patients with osteoporosis; some studies suggest that more benefit may be seen in pre-menopausal women.<sup>9,10</sup> Current research in bone remodeling has identified microRNAs (miRNAs), novel biomarkers with both diagnostic and therapeutic potential.<sup>11,12</sup> miRNAs are short, single stranded, non-coding RNAs which regulate posttranscriptional expression of mRNA.<sup>13</sup> miRNAs have been extensively implicated in bone remodeling and homeostasis. Circulating miRNAs have been shown to correlate with fragility fractures, and are conserved across subpopulations of osteoporotic patients.<sup>14-16</sup> miRNA panels have been suggested to have the potential to assist in diagnosis, prognosis, and are promising targets for directed therapy.<sup>13,15,17</sup> Although miRNAs have been investigated in conjunction with pre-menopausal, postmenopausal, idiopathic and diabetic osteoporosis, no research to date has explored the miRNA profile of PHPT patients with osteoporosis. Similarly, although in vitro experiments have demonstrated miRNA response to bisphosphonates,<sup>18</sup> no clear correlation has been established between therapeutic interventions and miRNA levels in vivo.<sup>15</sup> The goal of this study is therefore two-fold; first, to analyze the expression levels of circulating miRNAs in PHPT patients with and without osteoporosis; and second, to evaluate miRNA levels after treatment with parathyroidectomy.

References 1. Bone Health and Osteoporosis: A Report of the Surgeon General. Rockville MD2004. 2. Burge R, Dawson-Hughes B, Solomon DH, Wong JB, King A, Tosteson A. Incidence and economic burden of osteoporosis-related fractures in the United States, 2005-2025. Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research 2007;22:465-75. 3. Fraser WD. Hyperparathyroidism. Lancet (London, England) 2009;374:145-58. 4. Lewiecki EM, Miller PD. Skeletal effects of primary hyperparathyroidism: bone mineral density and fracture risk. Journal of

clinical densitometry : the official journal of the International Society for Clinical Densitometry 2013;16:28-32. 5. Walker MD, Silverberg SJ. Primary hyperparathyroidism. *Nature reviews Endocrinology* 2017. 6. De Geronimo S, Romagnoli E, Diacinti D, D'Erasmo E, Minisola S. The risk of fractures in postmenopausal women with primary hyperparathyroidism. *European journal of endocrinology* 2006;155:415-20. 7. Vignali E, Viccica G, Diacinti D, et al. Morphometric vertebral fractures in postmenopausal women with primary hyperparathyroidism. *The Journal of clinical endocrinology and metabolism* 2009;94:2306-12. 8. Bilezikian JP, Brandi ML, Eastell R, et al. Guidelines for the management of asymptomatic primary hyperparathyroidism: summary statement from the Fourth International Workshop. *The Journal of clinical endocrinology and metabolism* 2014;99:3561-9. 9. Lundstam K, Heck A, Godang K, et al. Effect of Surgery Versus Observation: Skeletal 5-Year Outcomes in a Randomized Trial of Patients With Primary HPT (the SIPH Study). *Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research* 2017;32:1907-14. 10. Lumachi F, Camozzi V, Ermani M, F DEL, Luisetto G. Bone mineral density improvement after successful parathyroidectomy in pre- and postmenopausal women with primary hyperparathyroidism: a prospective study. *Annals of the New York Academy of Sciences* 2007;1117:357-61. 11. Kim KM, Lim SK. Role of miRNAs in bone and their potential as therapeutic targets. *Current opinion in pharmacology* 2014;16:133-41. 12. Garnero P. New developments in biological markers of bone metabolism in osteoporosis. *Bone* 2014;66:46-55. 13. Jing D, Hao J, Shen Y, et al. The role of microRNAs in bone remodeling. *International journal of oral science* 2015;7:131-43. 14. Heilmeier U, Hackl M, Skalicky S, et al. Serum miRNA Signatures Are Indicative of Skeletal Fractures in Postmenopausal Women With and Without Type 2 Diabetes and Influence Osteogenic and Adipogenic Differentiation of Adipose Tissue-Derived Mesenchymal Stem Cells In Vitro. *Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research* 2016;31:2173-92. 15. Kocijan R, Muschitz C, Geiger E, et al. Circulating microRNA Signatures in Patients With Idiopathic and Postmenopausal Osteoporosis and Fragility Fractures. *The Journal of clinical endocrinology and metabolism* 2016;101:4125-34. 16. Weilner S, Skalicky S, Salzer B, et al. Differentially circulating miRNAs after recent osteoporotic fractures can influence osteogenic differentiation. *Bone* 2015;79:43-51. 17. Hackl M, Heilmeier U, Weilner S, Grillari J. Circulating microRNAs as novel biomarkers for bone diseases - Complex signatures for multifactorial diseases? *Molecular and cellular endocrinology* 2016;432:83-95. 18. Zhou Q, Zhao ZN, Cheng JT, et al. Ibandronate promotes osteogenic differentiation of periodontal ligament stem cells by regulating the expression of microRNAs. *Biochemical and biophysical research communications* 2011;404:127-32.

## ***Study Design***

### **Phase\***

Not applicable

### **Design**

This is a non-randomized cohort study. Subjects with and without osteoporosis, undergoing neck surgery or non-operative management will be recruited by one of two methods: 1. Prospectively identified and consented from the Endocrine Surgery and Endocrinology Clinics at the University of Pennsylvania Health System OR 2. Identified from the Penn Biobank (previously enrolled and consented). Patients will be matched for age and gender. Groups will consist of 25 subjects each, for a total study population of 100 subjects. Group 1: PHPT subjects with osteoporosis undergoing parathyroidectomy Group 2: PHPT subjects without osteoporosis undergoing parathyroidectomy Group 3: Subjects with benign thyroid disease and osteoporosis undergoing thyroid surgery Group 4: PHPT subjects with osteoporosis not undergoing surgery.

### **Study duration**

Estimated length of time to enroll all subjects and complete the study: 2 years Length of a subject's participation time in study: 2 years Projected start date of the proposed study: April 1, 2018

### **Resources necessary for human research protection**

Describe research staff and justify that the staff are adequate in number and qualifications to conduct the research. Describe how you will ensure that all staff assisting with the research are adequately informed about the protocol and their research related duties. Please allow adequate time for the researchers to conduct and complete the research. Please confirm that there are adequate facilities for the research.

Subjects will be recruited in one of two methods: 1. Prospectively identified and consented from the Endocrine Surgery and Endocrinology Clinics at the University of Pennsylvania Health System OR 2. Identified from the Penn Biobank (previously enrolled and consented). 1. Prospective subject recruitment and consenting will take place in the Endocrinology or Endocrine Surgery clinics of the University of Pennsylvania Health System under the supervision of the PI. Research staff will be CITI and HIPAA trained and will be required to review study protocols and be added to the IRB prior to participation. Serum samples will be obtained in the clinical laboratories of the University of Pennsylvania Health System. Standard serum testing will be performed in the clinical laboratories of the University of Pennsylvania Health System. Serum specimens for miRNA will be assigned a study identifier, all PHI will be removed, and specimens will be stored in -80 freezers in the Harrison Department of Surgical Research. Deidentified serum specimens will be processed commercially for miRNA. 2. The Penn Medicine BioBank specimens are collected with informed consent consistent with previously approved IRB protocols (IRB#813913 & IRB#817977). Human subject protection relates to subject confidentiality because there is no direct patient contact for this study. All study personnel have received the appropriate CITI training and are experienced in the conduct of research with human subjects. Appropriate computer security measures are in place; no PHI identifiers will be shared on these specimens. Data will be provided de-identified and specimens will be coded.

## **Characteristics of the Study Population**

### **Target population**

This study is a non-randomized cohort study comparing serum miRNA levels in patients undergoing neck surgery (parathyroidectomy or thyroidectomy) or medical management, with or without osteoporosis. We aim to enroll 25 patients in each of 4 groups: Group 1: PHPT subjects with osteoporosis undergoing parathyroidectomy Group 2: PHPT subjects without osteoporosis undergoing parathyroidectomy Group 3: Subjects with benign thyroid disease and osteoporosis undergoing thyroid surgery Group 4: PHPT subjects with osteoporosis not undergoing surgery.

### **Subjects enrolled by Penn Researchers**

100

### **Subjects enrolled by Collaborating Researchers**

0

### **Accrual**

Study subjects will be identified by one of two methods: 1. Prospectively identified and consented from the Endocrine Surgery and Endocrinology Clinics at the University of Pennsylvania Health System OR 2. Identified from the Penn Medicine BioBank (previously enrolled and consented). 1. Prospective study recruitment and consenting will take place in the Endocrine Surgical clinics of Drs. Wachtel, Kelz and Fraker in the Division of Endocrine and Oncologic Surgery or Endocrinology Clinic of Dr. Mona Al Mukaddam, Director of the Penn Bone center. Approximately 40-50 new patients with thyroid/parathyroid disorders are seen weekly in the combined surgical clinics. 2. Potential subjects from the Penn Medicine BioBank will be initially identified by data collected as part of the Penn Medicine BioBank protocols. The BioBank contains ~50,000 subjects. Future use of samples and personal health information has already been contemplated by participants of both parent protocols, thus there is no need to re-consent participants. We aim to enroll 25 patients in each of the 4 groups. A minimum group size of 17 is calculated to detect a 1 standard deviation difference in means assuming a two-sided alpha of 0.05 and beta 0.20, with equal variance of miRNA between groups; an enrollment of 25 patients will allow for potential attrition due to loss of follow up.

### **Key inclusion criteria**

Inclusion criteria: Adult patients with primary hyperparathyroidism undergoing parathyroidectomy; adult patients with benign thyroid disease and osteoporosis, undergoing thyroid surgery.

### **Key exclusion criteria**

Minors; vulnerable populations including adults unable to give consent; patients with thyroid malignancy; subjects with secondary osteoporosis including but not limited to renal osteodystrophy, hepatic dysfunction, glucocorticoid use, Cushings disease/syndrome, current or past use of bone active agents; use of estrogens or HRT; hyper- or hypothyroidism; vitamin d deficiency.

## **Vulnerable Populations**

**Children Form**

**Pregnant women (if the study procedures may affect the condition of the pregnant woman or fetus)  
Form**

**Fetuses and/or Neonates Form**

**Prisoners Form**

**Other x None of the above populations are included in the  
research study**

**The following documents are currently attached to this item:**

*There are no documents attached for this item.*

### **Populations vulnerable to undue influence or coercion**

Although not directly targeted, mentally disabled persons, economically or educationally disadvantaged persons, and/or employees or students of the University of Pennsylvania will not be denied enrollment and any special protections and/or additional safeguards will be undertaken in order to protect the rights and welfare of these subjects from coercion or undue influence as appropriate

### **Subject recruitment**

Study subjects will be identified by one of two methods: 1. Prospectively identified and consented from the Endocrine Surgery and Endocrinology Clinics at the University of Pennsylvania Health System OR 2. Identified from the Penn Medicine BioBank (previously enrolled and consented). 1. Prospectively identified and consented from the Endocrine Surgery and Endocrinology Clinics at the University of Pennsylvania Health System. a. During the subject's initial clinical consultation, the treating physician will describe the study and its risks and benefits. b. The potential subject will be given a copy of the consent form to review and have all questions answered. If the subject decides to participate, the principal investigator or member of the study team will obtain consent. c. The subjects will continue medical or surgical treatment with no alterations in their clinical care outside of venipuncture. 2. Subjects previously enrolled in the Penn Medicine BioBank will be assessed for eligibility. If meeting criteria for eligibility, they will be recontacted (recontact has previously been approved per BioBank protocol) for study enrollment.

Will the recruitment plan propose to use any Penn media services (communications, marketing, etc.) for outreach via social media avenues (examples include: Facebook, Twitter, blogging, texting, etc.) or does the study team plan to directly use social media to recruit for the research?

No

**The following documents are currently attached to this item:**

*There are no documents attached for this item.*

### **Subject compensation\***

Will subjects be financially compensated for their participation?

No

**The following documents are currently attached to this item:**

*There are no documents attached for this item.*

**If there is subject compensation, provide the schedule for compensation per study visit or session and total amount for entire participation, either as text or separate document**

No cash compensation will be offered to subjects. Parking vouchers will be provided for parking at Penn garages on the day of study visits, up to a total cost of \$13.00/day.

# Study Procedures

## Suicidal Ideation and Behavior

Does this research qualify as a clinical investigation that will utilize a test article (ie- drug or biological) which may carry a potential for central nervous system (CNS) effect(s)?

No

## Procedures

Please see attached protocol.

**The following documents are currently attached to this item:**

*There are no documents attached for this item.*

## Deception

Does your project use deception?

No

## International Research

Are you conducting research outside of the United States?

No

## Analysis Plan

Group comparisons will be performed to identify differences in clinical markers of bone remodeling and serum miRNA expression profiles in hyperparathyroid patients based on the presence of osteoporosis. Group comparisons will utilize the Students t test, Wilcoxon rank-sum test, and Fishers exact test, as appropriate. Pre- and postoperative clinical markers of bone remodeling and serum miRNA expression profiles will be compared using the chi-square test to identify treatment effect of parathyroidectomy or thyroidectomy.

**The following documents are currently attached to this item:**

*There are no documents attached for this item.*

## Data confidentiality

**Paper-based records will be kept in a secure location and only be accessible to personnel involved in the study.**

**x Computer-based files will only be made available to personnel involved in the study through the use of access privileges and passwords.**

**x Prior to access to any study-related information, personnel will be required to sign statements agreeing to protect the security and confidentiality of identifiable information.**

**x Wherever feasible, identifiers will be removed from study-related information.**

**A Certificate of Confidentiality will be obtained, because the research could place the subject at risk of criminal or civil liability or cause damage to the subject's financial standing, employability, or liability.**

**A waiver of documentation of consent is being requested, because the only link between the subject and the study would be the consent document and the primary risk is a breach of confidentiality. (This is not an option for FDA-regulated research.)**

**Precautions are in place to ensure the data is secure by using passwords and encryption, because the research involves web-based surveys.**

**Audio and/or video recordings will be transcribed and then destroyed to eliminate audible identification of subjects.**

## Subject Confidentiality

The identifiers used in this study are name, MRN, telephone number, date of birth, and date of surgery. Data will be deidentified (name and MRN removed from the dataset), and subjects will be assigned a study ID at the time of surgery. This will be kept on a secure, password protected, encrypted computer on the



Penn Medicine Server in a locking office in the Department of Surgery by the Principal Investigator. The linking dataset will be accessed to reidentify patients 1 year after surgery to obtain follow up clinical assessment and serum studies. Deidentified data will be entered into a REDCap database maintained by the University of Pennsylvania IT department.

**Sensitive Research Information\***

Does this research involve collection of sensitive information about the subjects that should be excluded from the electronic medical record?

No

**Subject Privacy**

Privacy refers to the person's desire to control access of others to themselves. Privacy concerns people, whereas confidentiality concerns data. Describe the strategies to protect privacy giving consideration to the following: The degree to which privacy can be expected in the proposed research and the safeguards that will be put into place to respect those boundaries. The methods used to identify and contact potential participants. The settings in which an individual will be interacting with an investigator. The privacy guidelines developed by relevant professions, professional associations and scholarly disciplines (e.g., psychiatry, genetic counseling, oral history, anthropology, psychology).

Subjects will be identified and consented by HIPAA and CITI trained investigators listed under Personnel. Subject recruitment, consent discussion and study procedures will be performed in dedicated clinical space at the University of Pennsylvania, with existing private exam and procedure rooms consistent with clinical practice. Per study protocol, subjects will be contacted by indicated telephone preference, 1 year after treatment or surgery to schedule follow up clinical and biochemical assessment.

**Data Disclosure**

Will the data be disclosed to anyone who is not listed under Personnel? No  
data will be disclosed to anyone who is not listed under Personnel.

**Data Protection\***

☒ Name

Street address, city, county, precinct, zip code, and equivalent geocodes ☒ All elements of dates  
(except year) for dates directly related to an individual and all ages over 89 ☒ Telephone and fax  
number

Electronic mail addresses

Social security numbers

☒ Medical record numbers

Health plan ID numbers

Account numbers

Certificate/license numbers

Vehicle identifiers and serial numbers, including license plate numbers

Device identifiers/serial numbers

Web addresses (URLs)

Internet IP addresses

Biometric identifiers, incl. finger and voice prints

Full face photographic images and any comparable images

Any other unique identifying number, characteristic, or code

None

Does your research request both a waiver of HIPAA authorization for collection of patient information and involve providing Protected Health Information ("PHI") that is classified as a "limited data set" (city/town/state/zip code, dates except year, ages less than 90 or aggregate report for over 90) to a recipient outside of the University of Pennsylvania covered entity?



No

**Tissue Specimens Obtained as Part of Research\* Are**

Tissue Specimens being obtained for research?

Yes

**Tissue Specimens - Collected during regular care\***

Will tissue specimens be collected during regular clinical care (for treatment or diagnosis)? Yes

**Tissue Specimens - otherwise discarded\***

Would specimens otherwise be discarded?

No

**Tissue Specimens - publicly available\* Will**

tissue specimens be publicly available?

No

**Tissue Specimens - Collected as part of research protocol\* Will**

tissue specimens be collected as part of the research protocol? Yes

**Tissue Specimens - Banking of blood, tissue etc. for future use\* Does**

research involve banking of blood, tissue, etc. for future use?

Yes

**Genetic testing**

If genetic testing is involved, describe the nature of the tests, including if the testing is predictive or exploratory in nature. If predictive, please describe plan for disclosing results to subjects and provision of genetic counseling. Describe how subject confidentiality will be protected Note: If no genetic testing is to be obtained, write: "Not applicable."

Not applicable

## Consent

### *1. Consent Process*

**Overview**

Prospective participant will be identified in Endocrinology or Endocrine Surgery clinics at the University of Pennsylvania Health System at the time of clinical consultation, or identified via the Penn Medicine BioBank. Subjects who are eligible for enrollment will be informed of the study and asked if they would like to participate by surgical staff. Sample consent language is below: "You are eligible for inclusion in a research study which examines the impact of surgery on bone health. Are you interested in hearing more information? Participation is completely voluntary, and will not change your medical or surgical care." If potential subjects are interested, formal consent form will be reviewed with patient (see attached document) by principle study investigator, Dr. Wachtel. This may be performed over the phone or in person at the time of the initial clinical consultation. Subjects who are incapable of consent will not be included in this study. Participants may choose to withdraw from the study at any time.

**Children and Adolescents**

Children and adolescents will not be included in this study.

**Adult Subjects Not Competent to Give Consent**

Adult subjects unable to give informed consent will not be included in this study.

### *2. Waiver of Consent*

**Waiver or Alteration of Informed Consent\***

No Waiver Requested

**Minimal Risk\*****Impact on Subject Rights and Welfare\*****Waiver Essential to Research\*****Additional Information to Subjects****Written Statement of Research\***

No

**If no written statement will be provided, please provide justification**

**The following documents are currently attached to this item:**

*There are no documents attached for this item.*

## **Risk / Benefit**

**Potential Study Risks**

The primary risk of this study is associated with an additional blood draw. Whenever possible, the blood draw will be combined with other required laboratory work, such as preoperative blood work. The risks are limited to pain at the phlebotomy site, swelling, or minimal risk of infection. The secondary risk of this study is a risk to loss of confidentiality, however the following measures will be taken to minimize this risk. The identifiers used in this study (MRN, name, DOS) will be used to identify the patient population of interest. During the identification of subjects, identifiers will be stored on a secure server on password-protected UPHS computers in a locking office in the Department of Surgery. After enrollment, data will be de-identified (MRN, name removed) and subjects will be assigned a study ID, and a linking dataset will be generated. This will be kept separately by PI on a password protected encrypted computer in a locking office in the Department of Surgery. De-identified data will be entered into a REDCap database. One year after surgery, subjects will be re-identified to facilitate contact for 1 year follow up visit. No patient information will be disclosed.

**Potential Study Benefits**

This study has no direct benefits to the individual subjects. This study has the potential to identify subpopulations who may benefit from early surgical intervention for primary hyperparathyroidism, and may change management guidelines for primary hyperparathyroidism.

**Alternatives to Participation (optional)**

Participation is entirely voluntary. Subjects may refuse to participate or withdraw from the study at any time with no repercussions.

**Data and Safety Monitoring**

This study will be monitored by the Principal Investigator.

**The following documents are currently attached to this item:**

*There are no documents attached for this item.*

**Risk / Benefit Assessment**

The risk of participation in this research is limited to an additional blood draw; whenever possible, this will be combined with other lab work to minimize discomfort to the subject. This study offers no direct benefit and only minimal risk to the subjects. There is significant societal benefit, however, as a better understanding of the genetic, molecular, and cellular events leading to the development of vascular disease will ultimately lead to the development of novel target strategies to prevent and treat vascular disease. As such, the minimal risk to the subjects is outweighed by the potential societal benefit.

## General Attachments

*The following documents are currently attached to this item:*

Cover Letter (irbrevisionscoverletter7.30.18.docx) Additional forms  
(study\_procedures\_circulating\_mirnas\_phpt.july2018.docx) Additional forms  
(study\_procedures\_circulating\_mirnas\_phpt.july2018.cleancopy.docx)  
Additional forms (pra\_template\_non-drug\_device\_intervention.parathyroid.mirna.7.24.18.xls)